L1 ANSWER 2 OF 12 REGISTRY COPYRIGHT 1999 ACS
RN 229480-65-3 REGISTRY
CN Protein (human clone HMEAA94 316-amino acid) (9CI) (CA INDEX NAME)
OTHER NAMES:
CN **FK506-binding protein homolog (human clone HMEAA94)**
FS PROTEIN SEQUENCE
MF Unspecified
CI MAN
SR CA
LC STN Files: CA, CAPLUS

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
*** USE 'SQD' OR 'SQIDE' FORMATS TO DISPLAY SEQUENCE ***
1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 131:84559

L1 ANSWER 3 OF 12 REGISTRY COPYRIGHT 1999 ACS
RN 229480-59-5 REGISTRY
CN Protein (human clone HFKBC47 C-terminal fragment) (9CI) (CA INDEX NAME)
OTHER NAMES:
CN **FK506-binding protein homolog (human clone HFKBC47 C-terminal fragment)**
FS PROTEIN SEQUENCE
MF Unspecified
CI MAN
SR CA
LC STN Files: CA, CAPLUS

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
*** USE 'SQD' OR 'SQIDE' FORMATS TO DISPLAY SEQUENCE ***
1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 131:84559

L1 ANSWER 4 OF 12 REGISTRY COPYRIGHT 1999 ACS
RN 229480-57-3 REGISTRY
CN Protein (human clone HSYBM46 541-amino acid precursor) (9CI) (CA INDEX NAME)
OTHER NAMES:
CN **FK506-binding protein homolog (human clone HSYBM46 precursor)**
FS PROTEIN SEQUENCE
MF Unspecified
CI MAN
SR CA
LC STN Files: CA, CAPLUS

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
*** USE 'SQD' OR 'SQIDE' FORMATS TO DISPLAY SEQUENCE ***
1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 131:84559

L1 ANSWER 5 OF 12 REGISTRY COPYRIGHT 1999 ACS
RN 229480-55-1 REGISTRY
CN Protein (human clone HL1AP03 C-terminal fragment) (9CI) (CA INDEX NAME)
OTHER NAMES:

CN **FK506-binding protein homolog (human clone HL1AP03 C-terminal fragment)**
FS PROTEIN SEQUENCE
MF Unspecified
CI MAN
SR CA
LC STN Files: CA, CAPLUS

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
*** USE 'SQD' OR 'SQIDE' FORMATS TO DISPLAY SEQUENCE ***
1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 131:84559

L1 ANSWER 6 OF 12 REGISTRY COPYRIGHT 1999 ACS
RN 229480-53-9 REGISTRY
CN Protein (human clone HMEAA94 316-amino acid precursor) (9CI) (CA INDEX NAME)
OTHER NAMES:
CN **FK506-binding protein homolog (human clone HMEAA94 precursor)**
FS PROTEIN SEQUENCE
MF Unspecified
CI MAN
SR CA
LC STN Files: CA, CAPLUS

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
*** USE 'SQD' OR 'SQIDE' FORMATS TO DISPLAY SEQUENCE ***
1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 131:84559

L1 ANSWER 7 OF 12 REGISTRY COPYRIGHT 1999 ACS
RN 223507-08-2 REGISTRY
CN FKBP12.6 protein (Mus musculus I.M.A.G.E. Consortium clone 390134 FKBP12.6) (9CI) (CA INDEX NAME)
OTHER NAMES:
CN **FK506-binding protein 12.6 (mouse)**
CN GenBank AF060872-derived protein GI 3777533
FS PROTEIN SEQUENCE
MF Unspecified
CI MAN
SR CA
LC STN Files: CA, CAPLUS, TOXLIT

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
*** USE 'SQD' OR 'SQIDE' FORMATS TO DISPLAY SEQUENCE ***
1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 130:307324

L1 ANSWER 8 OF 12 REGISTRY COPYRIGHT 1999 ACS
RN 216587-82-5 REGISTRY
CN Protein FKBP/SMAP (FK506-binding/smooth muscle activating) (chicken C-terminal fragment) (9CI) (CA INDEX NAME)
OTHER NAMES:
CN **FK506-binding/smooth muscle activating protein (Gallus gallus C-terminal fragment)**

CN GenBank AB008675-derived protein GI 3928515
FS PROTEIN SEQUENCE
MF Unspecified
CI MAN
SR CA
LC STN Files: CA, CAPLUS

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
*** USE 'SQD' OR 'SQIDE' FORMATS TO DISPLAY SEQUENCE ***
1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 130:35864

L1 ANSWER 9 OF 12 REGISTRY COPYRIGHT 1999 ACS
RN 207692-85-1 REGISTRY
CN Immunophilin (Arabidopsis thaliana gene PAS1-D) (9CI) (CA INDEX NAME)
OTHER NAMES:
CN **FK506-binding protein (Arabidopsis thaliana gene PAS1-D)**
CN GenBank U77366-derived protein GI 3080740
FS PROTEIN SEQUENCE
MF Unspecified
CI MAN
SR CA
LC STN Files: CA, CAPLUS

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
*** USE 'SQD' OR 'SQIDE' FORMATS TO DISPLAY SEQUENCE ***
1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 129:14421

L1 ANSWER 10 OF 12 REGISTRY COPYRIGHT 1999 ACS
RN 207692-84-0 REGISTRY
CN Immunophilin (Arabidopsis thaliana gene PAS1-A) (9CI) (CA INDEX NAME)
OTHER NAMES:
CN **FK506-binding protein (Arabidopsis thaliana gene PAS1-A)**
CN GenBank U77365-derived protein GI 3080738
FS PROTEIN SEQUENCE
MF Unspecified
CI MAN
SR CA
LC STN Files: CA, CAPLUS

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
*** USE 'SQD' OR 'SQIDE' FORMATS TO DISPLAY SEQUENCE ***
1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 129:14421

L1 ANSWER 11 OF 12 REGISTRY COPYRIGHT 1999 ACS
RN 190735-30-9 REGISTRY
CN Synthase, FK 506 (9CI) (CA INDEX NAME)
OTHER NAMES:
CN **FK506 polyketide synthase**
CN **FK506 synthase**
MF Unspecified
CI MAN
SR CA

LC STN Files: CA, CAPLUS, TOXLIT

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
               2 REFERENCES IN FILE CA (1967 TO DATE)
               2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 129:340416

REFERENCE 2: 127:30874

L1 ANSWER 12 OF 12 REGISTRY COPYRIGHT 1999 ACS
RN 158888-69-8 REGISTRY
CN Isomerase, peptidylprolyl cis-trans- (Streptomyces chrysomallus clone pAP2503 gene fkbB precursor) (9CI) (CA INDEX NAME)
OTHER NAMES:
CN **FK506-binding protein FKBP-33 (Streptomyces chrysomallus clone pAP2503)**
CN Protein FKBP 33 (Streptomyces chrysomallus clone pAP2503 FK 506-binding precursor)
FS PROTEIN SEQUENCE
MF Unspecified
CI MAN
SR CA
LC STN Files: CA, CAPLUS

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
*** USE 'SQD' OR 'SQIDE' FORMATS TO DISPLAY SEQUENCE ***
               1 REFERENCES IN FILE CA (1967 TO DATE)
               1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 121:276306

=> e "fkbp-12"/cn 5

E1   1   FKBP PROTEIN CBMIP (COXIELLA BURNETTI MACROPHAGE INFECTIVITY
                   POTENTIATOR 15.5-KILODALTON ANALOG)/CN
E2   1   FKBP, PROTEIN (XENOPUS LAEVIS)/CN
E3   0 --> FKBP-12/CN
E4   1   FKBP-TYPE PEPTIDYL-PROLYL CIS-TRANS ISOMERASE (CHLAMYDIA PNE
                  UMONIAE GENE MIP)/CN
E5   1   FKBP-TYPE PEPTIDYL-PROLYL CIS-TRANS ISOMERASE (CHLAMYDIA TRA
                  CHOMATIS GENE MIP)/CN

=> fil medl,caplus,biosis,embase,wpids

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	21.97	2148.68

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	0.00	-43.45

FILE 'MEDLINE' ENTERED AT 15:34:18 ON 01 NOV 1999

FILE 'CAPLUS' ENTERED AT 15:34:18 ON 01 NOV 1999
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.

PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

FILE 'BIOSIS' ENTERED AT 15:34:18 ON 01 NOV 1999

FILE 'EMBASE' ENTERED AT 15:34:18 ON 01 NOV 1999

FILE 'WPIDS' ENTERED AT 15:34:18 ON 01 NOV 1999

=> s l1 or fk506 or fk 506

L2 3340 FILE MEDLINE
L3 3216 FILE CAPLUS
L4 4408 FILE BIOSIS
L5 4953 FILE EMBASE
L6 212 FILE WPIDS

TOTAL FOR ALL FILES
L7 16129 L1 OR FK506 OR FK 506

=> s tacrolim? or prograf?

L8 3787 FILE MEDLINE
L9 708 FILE CAPLUS
L10 1461 FILE BIOSIS
L11 1376 FILE EMBASE
L12 15 FILE WPIDS

TOTAL FOR ALL FILES
L13 7347 TACROLIM? OR PROGRAF?

=> s fkbp 12 or fk506 bind? protein 12

L14 94 FILE MEDLINE
L15 248 FILE CAPLUS
L16 158 FILE BIOSIS
L17 104 FILE EMBASE
L18 9 FILE WPIDS

TOTAL FOR ALL FILES
L19 613 FKBP 12 OR FK506 BIND? PROTEIN 12

=> s (l7 or l13) and l19 and (screen? or assay?) and nerve cell

L20 0 FILE MEDLINE
L21 0 FILE CAPLUS
L22 0 FILE BIOSIS
L23 0 FILE EMBASE
L24 1 FILE WPIDS

TOTAL FOR ALL FILES
L25 1 (L7 OR L13) AND L19 AND (SCREEN? OR ASSAY?) AND NERVE CELL

=> d

L25 ANSWER 1 OF 1 WPIDS COPYRIGHT 1999 DERWENT INFORMATION LTD
AN 1999-312859 [26] WPIDS

DNC C1999-092323
TI Stimulation of **nerve cell** growth to treat neurological conditions involving neuronal dysfunction.
DC B05 D16
IN GOLD, B G
PA (UYOR-N) UNIV OREGON HEALTH SCI
CYC 82
PI WO 9921552 A1 19990506 (199926)* EN 52p A61K031-395
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH GM HR HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW
AU 9896783 A 19990517 (199939) A61K031-395
ADT WO 9921552 A1 WO 1998-US20658 19981002; AU 9896783 A AU 1998-96783 19981002
FDT AU 9896783 A Based on WO 9921552
PRAI US 1997-956691 19971024
IC ICM A61K031-395

=> s (l7 or l13 or l19) and (screen? or assay?) and nerve cell

L26 0 FILE MEDLINE
L27 0 FILE CAPLUS
L28 0 FILE BIOSIS
L29 1 FILE EMBASE
L30 1 FILE WPIDS

TOTAL FOR ALL FILES
L31 2 (L7 OR L13 OR L19) AND (SCREEN? OR ASSAY?) AND NERVE CELL

=> dup rem l31

PROCESSING COMPLETED FOR L31
L32 2 DUP REM L31 (0 DUPLICATES REMOVED)

=> d 1-2 cbib abs

L32 ANSWER 1 OF 2 WPIDS COPYRIGHT 1999 DERWENT INFORMATION LTD
AN 1999-312859 [26] WPIDS
AB WO 9921552 A UPAB: 19990707
NOVELTY - Method of stimulating **nerve cell** growth in subjects comprises administration of a compound that disrupts assembly of a steroid receptor complex, excluding estrogen, androgen or recognized compound that binds to immunophilin **FKBP-12**, without side effects such as immunosuppression, and cardiomyopathy, is new.
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:
(1) methods of **screening** for compound that stimulates **nerve cell** growth; and
(2) pharmaceutical compositions containing nerve growth stimulating amount of an agent that binds to a poly peptide of a steroid receptor complex other than a steroid hormone binding portion of the complex.
ACTIVITY - Neurotrophic. Neuroblastoma SH-SY5Y cells were used to examine human neurite outgrowth in vitro. The results showed that **FK506** increases neurite outgrowth in SH0-SY5Y cells in a concentration-dependent manner. Cumulative histograms of neurite lengths showed that 10 pM-10 nM F506 significantly increased neurite outgrowth

(Mann-Whitney U test (alpha =0.05)). However, 100 nM was less effective and, at 1000 nM or greeter concentrations, neurite outgrowth was inhibited.

MECHANISM OF ACTION - Steroid-receptor complex assembly disruption.

USE - Used to treat animals with neurological conditions associated with neuronal dysfunction caused by disease or injury to neurons, including animals with injury to a neuron of the central or peripheral nervous system (claimed). Used also in association with procedures such as surgical nerve grafts or other implantations of neurological tissue to promote healing of the graft or implant and promote incorporation of the graft or implant into neurological tissue.

Used to promote neuronal regeneration and functional recovery and to stimulate neurite outgrowth in the threatment of neuropathological states such as damage to peripheral nerves and the central nervous system caused by physical injury (e.g. spinal cord injury and trauma, sciatic or facial nerve lesion or injury, limb transplantation following amputation), disease (e.g. diabetic neuropathy), cancer chemotherapy (neuropathy induced by acrylamide, taxol, vinca alkaloids and doxorubicin), brain damaged associated with stroke and ischemia, and neurological disorders including peripheral neuropathic and neurological disorders related to neurodegeneration including trigeminal neuralgia, glossopharyngeal neuralgia, Bell's palsy, myasthenia gravis, muscular dystrophy, amyotrophic lateral sclerosis, progressive muscular atrophy, progressive bulbar inherited muscular dystrophy, herniated, ruptured or prolapsed vertebral disc syndromes, cervical spondylosis, plexus disorders, thoracic outlet destruction syndromes, peripheral neuropathies caused by lead, acrylamides, gamma diketones (glue-sniffer's neuropathy), carbon disulfide, dapsone, ticks, porphyria, Gullain-Barre syndrome, Alzheimer's disease, Parkinson's disease and Huntington's chorea.

Also used in prevention and treatment of stroke and connective tissue disorders and as a male contraceptive.

ADVANTAGE - Compounds need not have significant calcineurin inhibition or rotamase inhibition. Avoids unwanted side-effects of prior-art methods e.g. immunosuppression and cardiomyopathy.

L32 ANSWER 2 OF 2 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.

96319713 EMBASE Document No.: 1996319713. Okadaic acid suppresses neural differentiation-dependent expression of the neurofilament-L gene in P19 embryonal carcinoma cells by post- transcriptional modification. Sasahara Y.; Kobayashi T.; Onodera H.; Onoda M.; Ohnishi M.; Kato S.; Kusuda K.; Shima H.; Nagao M.; Abe H.; Yanagawa Y.; Hiraga A.; Tamura S.. Dept. of Biochemistry, IDAC, Tohoku University, 4-1 Seiryomachi,Aoba-ku, Sendai 980, Japan. Journal of Biological Chemistry 271/42 (25950-25957) 1996. ISSN: 0021-9258. CODEN: JBCHA3. Pub. Country: United States. Language: English. Summary Language: English.

AB Mouse P19 embryonal carcinoma cells in aggregation culture in the presence of 10-6 M retinoic acid followed by monolayer culture differentiate into nerve and glial cells. In this study, we demonstrated that the neurofilament-L (NF-L) mRNA and protein levels of these cells were enhanced in accordance with their retinoic acid-induced neural differentiation. Okadaic acid (OA) treatment of the cells markedly suppressed this differentiation-dependent NF-L gene expression increase and neurite outgrowth of the cells. Similar results were obtained when tautomycin was used instead of OA, suggesting that inhibition of protein phosphatase(s) is involved in the suppression of neural differentiation. OA treatment did not affect the NF-L gene transcription level, determined by the nuclear run-on transcription **assay**, but it did reduce the

stability of both the 3.5- and 2.3-kilobase NF-L mRNAs. The expression and activity levels of protein phosphatase 2A (PP2A) and 2B (PP2B) but not protein phosphatase 1 (PP1) in P19 cells increased in accordance with the enhanced NF-L gene expression. The presence of OA in the culture medium during the course of the neural differentiation caused a reduced PP2A activity but not PP1 and PP2B activities of the cell extracts. On the other hand, both PP1 and PP2B activities but not PP2A activity of cell extracts were suppressed by the addition of cyclosporin A or **FK506** in the culture medium. However, both cyclosporin A and **FK506** treatments affected neither NF-L gene expression nor neurite outgrowth. These results demonstrate that the OA treatment inhibits the differentiation-dependent increase in NF-L gene expression by destabilizing its mRNAs and suggest that PP2A plays key roles in the differentiation-dependent enhanced expression of the NF-L gene and is the point of the action of OA.

```
=> s gold b?/au,in and nerve regenerat?

'IN' IS NOT A VALID FIELD CODE
L33          12 FILE MEDLINE
L34          11 FILE CAPLUS
L35          11 FILE BIOSIS
'IN' IS NOT A VALID FIELD CODE
L36          10 FILE EMBASE
L37           0 FILE WPIDS

TOTAL FOR ALL FILES
L38          44 GOLD B?/AU,IN AND NERVE REGENERAT?

=> s (17 or 113 or 119) and 138

L39           8 FILE MEDLINE
L40          10 FILE CAPLUS
L41           9 FILE BIOSIS
L42           8 FILE EMBASE
L43           0 FILE WPIDS

TOTAL FOR ALL FILES
L44          35 (L7 OR L13 OR L19) AND L38

=> dup rem 144

PROCESSING COMPLETED FOR L44
L45          14 DUP REM L44 (21 DUPLICATES REMOVED)

=> d cbib abs 1-14


L45  ANSWER 1 OF 14  CAPLUS  COPYRIGHT 1999 ACS
1999:297301   Document No. 130:320857  Use of non-immunosuppressive compounds
      which disrupt the steroid receptor complex for promoting nerve
      regeneration, screening method, pharmaceutical compositions, and
      therapeutic use.  Gold, Bruce Gordon (Oregon Health Sciences
      University, USA).  PCT Int. Appl. WO 9921552 A1 19990506, 55 pp.
      DESIGNATED STATES: W:  AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH,
CN,
      CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE,
      KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO,
      NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US,
```

UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1998-US20658 19981002. PRIORITY: US 1997-956691 19971024.

AB This invention takes advantage of the finding that neurite outgrowth and **nerve regeneration** are promoted by disruption of the steroid receptor complex. This disruption can take the form of disruption of the phys. assembly or function of the steroid receptor complex, such as the mature complex or a precursor of the mature complex that is required for assembly of the mature complex. Geldanamycin and its analogs, as well as FKBP-52 antibody, are shown to disrupt the complex and promote nerve growth. In addn. to these compds., the invention includes assays for finding neurotrophic compds., as well as compds. found by these assays, pharmaceutical compns. into which they are incorporated, and methods of treating subjects having neuronal dysfunction caused by injury or disease.

L45 ANSWER 2 OF 14 MEDLINE DUPLICATE 1

1999269149 Document Number: 99269149. Immunophilin **FK506**-binding protein 52 (not **FK506-binding protein 12**) mediates the neurotrophic action of **FK506**. **Gold B G**; Densmore V; Shou W; Matzuk M M; Gordon H S. (Center for Research on Occupational and Environmental Toxicology, Oregon Health Sciences University, Portland, Oregon.. gold@ohsu.edu). JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, (1999 Jun) 289 (3) 1202-10. Journal code: JP3. ISSN: 0022-3565. Pub. country: United States. Language: English.

AB The neurotrophic property of the immunosuppressant drug **FK506** (**tacrolimus**) is believed to depend on the 12-kDa **FK506**-binding protein (**FKBP-12**). Here, we show that **FK506** maintains its neurotrophic activity in primary hippocampal cell cultures from **FKBP-12** knockout mice. In human neuroblastoma SH-SY5Y cells, the neurotrophic action of **FK506** (10 pM to 10 nM) is completely prevented by the addition of a monoclonal antibody (50-100 nM) to the immunophilin FKBP-52 (also known as FKBP-59 or heat shock protein 56), a component of mature steroid receptor complexes. By itself, the FKBP-52 antibody is also neurotrophic. The neurotrophic activity of dexamethasone (50 nM) is potentiated by **FK506**, whereas that of beta-estradiol (50 nM) is not altered, suggesting a common mechanisms of action. Geldanamycin (which disrupts mature steroid receptor complexes) is also neurotrophic (0.1-10 nM), whereas it reduces the neurotrophic activity of **FK506** and steroid hormones (dexamethasone and beta-estradiol). Conversely, 20 mM molybdate (which prevents the disruption of mature steroid receptor complexes) decreases the neurotrophic activity of **FK506**, FKBP-52 antibody, dexamethasone, and beta-estradiol. In rats, **FK506** (10 mg/kg s.c.) augments the regenerative response of regenerating motor and sensory neurons to nerve injury as shown by its ability to increase the axotomy-induced induction of c-jun expression. A model is proposed to account for the neurotrophic action of both neuroimmunophilin ligands (**FK506**) and steroid hormones. Components of steroid receptor complexes represent novel targets for the rational design of new

neurotrophic drugs.

L45 ANSWER 3 OF 14 MEDLINE DUPLICATE 2
1999390646 Document Number: 99390646. **FK506** and the role of the immunophilin FKBP-52 in **nerve regeneration. Gold B G.** (Department of Cell and Developmental Biology, Oregon Health Sciences University, Portland 97201, USA.)DRUG METABOLISM REVIEWS, (1999 Aug) 31 (3) 649-63. Ref: 75. Journal code: EBT. ISSN: 0360-2532. Pub. country: United States. Language: English.
AB In summary, **FKBP-12** does not mediate the neurite outgrowth-promoting properties of neuroimmunophilin ligands (e.g., **FK506**). Instead, the neurotrophic properties of neuroimmunophilin ligands (**FK506**) and steroid hormones are mediated by disruption of steroid-receptor complexes. It remains unclear which component mediates neurite outgrowth, although the most likely candidates are FKBP-52, hsp-90, and p23 [42]. Regardless of the underlying mechanism involved, the FKBP-52 antibody data reveal that it should be possible to design, based on the structure of **FK506**, non-**FKBP-12** -binding (nonimmunosuppressant) compounds selective for FKBP-52 and test these new libraries for their ability to augment **nerve regeneration**. It may also be possible to exploit the structure of geldanamycin to develop a new class of hsp-90-binding compounds for use in **nerve regeneration.**

L45 ANSWER 4 OF 14 CAPLUS COPYRIGHT 1999 ACS DUPLICATE 3
1999:340387 Document No. 131:125122 Efficacy of delayed or discontinuous **FK506** administrations on **nerve regeneration** in the rat sciatic nerve crush model: lack of evidence for a conditioning lesion-like effect. **Gold, Bruce G.**; Gordon, Heidi S.; Wang, M.-S. (Center for Research on Occupational and Environmental Toxicology, Oregon Health Sciences University, Portland, OR, 97201, USA). Neurosci. Lett., 267(1), 33-36 (English) 1999. CODEN: NELED5. ISSN: 0304-3940. Publisher: Elsevier Science Ireland Ltd..
AB We examd. whether the **nerve regenerative** property of **FK506** exhibits a 'window-of-opportunity' corresponding to the time of injury for maximal efficacy in the sciatic nerve crush model. **FK506** (5 mg/kg, s.c.) was administered over the 18-day period of study according to three dosage regiments: delayed (days 9-17), discontinuous (days 0-8) and continuous (days 0-17) administrations. Quantitation of axonal calibers and the extend of myelination in the soleus nerve at 18 days demonstrated that both delayed and discontinuous administrations were equally effective, arguing against a 'window-of-opportunity' for **FK506 nerve regenerative** effect. However, both protocols were less effective than continuous administration indicating that the compd. needs to be given during the entire regenerative period to elicit maximal efficacy.

L45 ANSWER 5 OF 14 BIOSIS COPYRIGHT 1999 BIOSIS
1999:52772 Document No.: PREV199900052772. Efficacy of delayed or discontinuous **FK506** administration on **nerve regeneration** in the sciatic nerve crush model: Lack of evidence for a conditioning lesion-like effect. Gordon, H. S.; Zeleny-Pooley, M.; Wang, M.-S.; **Gold, B. G.**. Cent. Res. Occup. Environ. Toxicol., Oreg. Health Sci. Univ., Portland, OR 97201 USA. Society for Neuroscience Abstracts, (1998) Vol. 24, No. 1-2, pp. 813. Meeting Info.: 28th Annual Meeting of the Society for Neuroscience, Part 1 Los Angeles, California, USA November 7-12, 1998 Society for Neuroscience. ISSN: 0190-5295. Language: English.

L45 ANSWER 6 OF 14 BIOSIS COPYRIGHT 1999 BIOSIS
1999:52771 Document No.: PREV199900052771. Identification of the **FK506** (neuroimmunophilin) target mediating **nerve regeneration** . **Gold, B. G. (1)**; Densmore, V.; Zeleny-Pooley, M.; Gordon, H. S.. (1) Dep. Cell Dev. Biol., Oreg. Health Sci. Univ., Portland, OR 97201 USA. Society for Neuroscience Abstracts, (1998) Vol. 24, No. 1-2, pp. 813.
Meeting Info.: 28th Annual Meeting of the Society for Neuroscience, Part 1
Los Angeles, California, USA November 7-12, 1998 Society for Neuroscience.
ISSN: 0190-5295. Language: English.

L45 ANSWER 7 OF 14 MEDLINE DUPLICATE 4
1998171359 Document Number: 98171359. Oral administration of a nonimmunosuppressant **FKBP-12** ligand speeds **nerve regeneration**. **Gold B G**; Zeleny-Pooley M; Chaturvedi P; Wang M S. (Center for Research on Occupational and Environmental Toxicology/L606 and Department of Cell and Developmental Biology, Oregon Health Sciences University, Portland 97201-3098, USA.)NEUROREPORT, (1998 Feb 16) 9 (3) 553-8. Journal code: A6M. ISSN: 0959-4965. Pub. country: ENGLAND: United Kingdom. Language: English.
AB We recently showed that s.c. injections of a nonimmunosuppressant **FK506 binding protein-12** (**FKBP-12**) ligand (V-10,367) accelerates **nerve regeneration** in the rat sciatic nerve crush model. Here we examined the oral efficacy of this compound for speeding **nerve regeneration**. Rats receiving V-10,367 (5, 15 or 50 mg/kg/day) by oral gavage all demonstrated an increase in **nerve regeneration** compared to vehicle-treated controls. Functional recovery was observed earliest and axonal calibers of regenerating axons in the soleus nerve were largest in the 15 mg/kg group, mean axonal areas being increased by 66% compared to controls. Orally active nonimmunosuppressant **FKBP-12** ligands may be useful for the treatment of human peripheral nerve disorders.

L45 ANSWER 8 OF 14 CAPLUS COPYRIGHT 1999 ACS
1998:545837 Document No. 129:183786 **Nerve regenerative** activity of the immunosuppressant **FK506** (**tacrolimus**). Katoh, Kiyoshi; **Gold, Bruce G.** (Sch. Nurs., Fukushima Med. Univ., Fukushima, 960-1247, Japan). Fukushima Igaku Zasshi, 48(2), 87-97 (Japanese) 1998. CODEN: FSIZAQ. ISSN: 0016-2582. Publisher: Fukushima Igakkai.
AB A review with 64 refs. **FK506** (**tacrolimus**), isolated from Streptomyces tsukubaensis, is an immunosuppressant which has more potent immunosuppressive activity and an overall lower incidence of adverse side effects than cyclosporin A. **FK506** is activated when bound to its binding protein (immunophilin), **FK506** -binding-protein (FKBP), in order to inhibit the activity of calcineurin. The inhibition leads to the prevention of induction of interleukin 11 secretion thereby preventing T-cell proliferation. Calcineurin is present also in nervous tissue and dephosphorylates the growth-assocd. protein GAP-43. Since GAP-43 plays an important role in **nerve regeneration**, we initiated a series of studies on the **nerve regenerative** activities of **FK506**, with an assumption that this particular immunosuppressant should alter **nerve regeneration**. Rats given daily s.c. injections of **FK506** (1 mg/kg) recovered the usefulness of the foot and moved the toes 2 days earlier than those of control animals after sciatic nerve

axotomy. Morphol. observations were also pos. correlated with the behavioral improvements. The maximal distance of axonal elongation from the crush site was measured using radiolabeling techniques, and we found that **FK506** significantly increased the axonal regeneration rate from 3.8 mm/day in control rats to 4.4 mm/day in **FK506**-treated animals. Dose-dependency for **nerve regenerative** effect of **FK506** was also obsd. and the best results were obtained in animals given the 5 mg/kg dose in the behavioral, morphol. observation and also by the measurements from radiolabeling techniques (i.e., 5.1 mm/day). It was assumed that cyclosporin A would also increase the rate of axonal regeneration, if calcineurin inhibition is the underlying mechanism for **FK506**'s **nerve regenerative** effect. However, this hypothesis was not supported exptl. In addn., **FKBP-12** ligands which do not inhibit calcineurin did increase the **nerve regeneration**. These findings suggest that the **nerve regenerative** capability of **FK506** is not related with the calcineurin-inhibiting activity. Furthermore, it remains possible that other FKBP's (i.e, FKBP-52), may mediate FKBP's **nerve regenerative** property. Although the mechanism by which **FK506** accelerates the rate of axonal regeneration is unclear, the studies with it's analogs will hopefully bring new perspectives for **nerve regeneration**. FKBP ligands also represent new mol. probes for studying intracellular signal transduction.

L45 ANSWER 9 OF 14 MEDLINE DUPLICATE 5

1998161312 Document Number: 98161312. The immunosuppressant **FK506** increases GAP-43 mRNA levels in axotomized sensory neurons. **Gold B G**; Yew J Y; Zeleny-Pooley M. (Center for Research on Occupational and Environmental Toxicology, Oregon Health Sciences University, Portland 97201, USA.)NEUROSCIENCE LETTERS, (1998 Jan 23) 241 (1) 25-8. Journal code: N7N. ISSN: 0304-3940. Pub. country: Ireland. Language: English.

AB **FK506**, an immunosuppressant drug used to prevent allograft rejection in organ transplantations, accelerates functional recovery and **nerve regeneration** in the rat sciatic nerve crush model. While the mechanism by which **FK506** increases regeneration is unknown, in contrast to immunosuppression, it does not involve calcineurin inhibition. Using the reverse-transcriptase polymerase chain reaction (RT-PCR) technique and a digoxigenin-labeled probe, we show that subcutaneous injections of **FK506** (10 mg/kg/day) markedly increases the level of axotomy-induced growth-associated protein (GAP-43) mRNA in dorsal root ganglion (DRG) neurons. Quantitation of DRG neurons revealed that **FK506** produced a 33% increase in the numbers of neurons exhibiting intense staining. Increased synthesis of GAP-43 may play a role in **FK506**'s ability to speed **nerve regeneration**.

L45 ANSWER 10 OF 14 MEDLINE DUPLICATE 6

97404292 Document Number: 97404292. Comparative dose-dependence study of **FK506** and cyclosporin A on the rate of axonal regeneration in the rat sciatic nerve. Wang M S; Zeleny-Pooley M; **Gold B G**. (Center for Research on Occupational and Environmental Toxicology, Oregon Health Sciences University, Portland 97201-3098, USA.)JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, (1997 Aug) 282 (2) 1084-93. Journal code: JP3. ISSN: 0022-3565. Pub. country: United States. Language: English.

AB The new immunosuppressant drug **FK506** (**Tacrolimus**) increases the rate of **nerve regeneration** in vivo (Gold et al., 1994; Gold et al., 1995). In the present study, we have examined

the dose-dependence of **FK506**'s ability to enhance **nerve regeneration**. In the first set of experiments, rats received daily s.c. injections of **FK506** (2 mg/kg, 5 mg/kg or 10 mg/kg) for 18 days after a sciatic nerve crush injury. Signs of functional recovery in the hind feet appeared earlier than in saline-treated control rats at all three **FK506** dosage; recovery was maximally accelerated in the 5-mg/kg group. Light microscopy at 18 days after nerve crush revealed more regenerating myelinated fibers in **FK506**-treated rats than in controls; this was most apparent in the 5-mg/kg group. Morphometric analysis of axonal areas in the soleus nerve confirmed that axonal calibers were maximally increased in the 5-mg/kg group. In the second set of experiments, the rate of axonal regeneration was determined by radiolabeling the L5 dorsal root ganglion. Regeneration rate for sensory axons was maximally increased (by 34%) in the 5-mg/kg group. In contrast, cyclosporin A (10 or 50 mg/kg; dosages were selected on the basis of the 1/10 lower potency of cyclosporin A) did not significantly alter the rate of axonal regeneration. Cyclosporin A (50 mg/kg) also failed to increase functional recovery or axonal calibers in the soleus nerve. Because the two drugs share a common mechanism for producing immunosuppression (i.e., calcineurin inhibition), these results indicate that **FK506**'s **nerve regenerative** property involves a distinct, calcineurin-independent mechanism.

L45 ANSWER 11 OF 14 MEDLINE DUPLICATE 7

1998119047 Document Number: 98119047. **FK506** and the role of immunophilins in **nerve regeneration**. **Gold B G**. (Center for Research on Occupational and Environmental Toxicology, Oregon Health Sciences University, Portland 97201, USA.)MOLECULAR NEUROBIOLOGY, (1997 Dec) 15 (3) 285-306. Ref: 178. Journal code: AH6. ISSN: 0893-7648. Pub. country: United States. Language: English.

AB **FK506** is a new FDA-approved immunosuppressant used for prevention of allograft rejection in, for example, liver and kidney transplantations. **FK506** is inactive by itself and requires binding to an **FK506 binding protein-12** (**FKBP-12**), or immunophilin, for activation. In this regard, **FK506** is analogous to cyclosporin A, which must bind to its immunophilin (cyclophilin A) to display activity. This **FK506**-FKBP complex inhibits the activity of the serine/threonine protein phosphatase 2B (calcineurin), the basis for the immunosuppressant action of **FK506**. The discovery that immunophilins are also present in the nervous system introduces a new level of complexity in the regulation of neuronal function. Two important calcineurin targets in brain are the growth-associated protein GAP-43 and nitric oxide (NO) synthase (NOS). This review focuses on studies showing that systemic administration of **FK506** dose-dependently speeds **nerve regeneration** and functional recovery in rats following a sciatic-nerve crush injury. The effect appears to result from an increased rate of axonal regeneration. The **nerve regenerative** property of this class of agents is separate from their immunosuppressant action because **FK506**-related compounds that bind to **FKBP-12** but do not inhibit calcineurin are also able to increase **nerve regeneration**. Thus, **FK506**'s ability to increase **nerve regeneration** arises via a calcineurin-independent mechanism (i.e., one not involving an increase in GAP-43 phosphorylation). Possible mechanisms of action are discussed in relation to known actions of FKBPs: the interaction of **FKBP-12** with two Ca2+ release-channels (the ryanodine and inositol 1,4,5-triphosphate receptors) which is disrupted by **FK506**, thereby increasing Ca2+ flux; the type 1 receptor for the transforming

growth factor-beta (TGF-beta 1), which stimulates nerve growth factor (NGF) synthesis by glial cells, and is a natural ligand for **FKBP -12**; and the immunophilin FKBP-52/FKBP-59, which has also been identified as a heat-shock protein (HSP-56) and is a component of the nontransformed glucocorticoid receptor. Taken together, studies of **FK506** indicate broad functional roles for the immunophilins in the nervous system. Both calcineurin-dependent (e.g., neuroprotection via reduced NO formation) and calcineurin-independent mechanisms (i.e., **nerve regeneration**) need to be invoked to explain the many different neuronal effects of **FK506**. This suggests that multiple immunophilins mediate **FK506**'s neuronal effects. Novel, nonimmunosuppressant ligands for FKBPs may represent important new drugs for the treatment of a variety of neurological disorders.

L45 ANSWER 12 OF 14 MEDLINE DUPLICATE 8
1998014503 Document Number: 98014503. A nonimmunosuppressant **FKBP-12** ligand increases **nerve regeneration.**
Gold B G; Zeleny-Pooley M; Wang M S; Chaturvedi P; Armistead D M. (Center for Research on Occupational and Environmental Toxicology and Department of Cell and Developmental Biology, Oregon Health Sciences University, Portland 97201-3098, USA.)EXPERIMENTAL NEUROLOGY, (1997 Oct) 147 (2) 269-78. Journal code: EQF. ISSN: 0014-4886. Pub. country: United States. Language: English.

AB The immunosuppressant drugs **FK506** and cyclosporin A inhibit T-cell proliferation via a common mechanism: calcineurin inhibition following binding to their respective binding proteins, the peptidyl prolyl isomerases **FKBP-12** and cyclophilin A. In contrast, **FK506**, but not cyclosporin A, accelerates **nerve regeneration**. In the present study, we show that the potent **FKBP-12** inhibitor V-10,367, which lacks the structural components of **FK506** required for calcineurin inhibition, increases neurite outgrowth in SH-SY5Y neuroblastoma cells and speeds **nerve regeneration** in the rat sciatic nerve crush model. In SH-SY5Y cells, V-10,367 increased the lengths of neurite processes in a concentration-dependent (between 1 and 10 nM) fashion over time (up to 168 h). Daily subcutaneous injections of V-10,367 accelerated the onset of clinical signs of functional recovery in the hind feet compared to vehicle-treated control animals. Interdigit distances (between the first and fifth digits) measured on foot prints obtained during walking showed an increase in toe spread in V-10,367-treated rats compared to vehicle-treated controls. Electron microscopy demonstrated larger regenerating axons distal to the crush site in the sciatic nerve from V-10,367-treated rats. Quantitation of axonal areas in the soleus nerve revealed a shift to larger axonal calibers in V-10,367-treated rats (400 or 200 mg/kg/day); mean axonal areas were increased by 52 and 59%, respectively, compared to vehicle-treated controls. **FKBP-12** ligands lacking calcineurin inhibitory activity represent a new class of potential drugs for the treatment of human peripheral nerve disorders.

L45 ANSWER 13 OF 14 MEDLINE
96066773 Document Number: 96066773. The immunosuppressant **FK506** increases the rate of axonal regeneration in rat sciatic nerve. **Gold B G**; Katoh K; Storm-Dickerson T. (Center for Research on Occupational and Environmental Toxicology, Oregon Health Sciences University, Portland 97201-3098, USA..)JOURNAL OF NEUROSCIENCE, (1995 Nov) 15 (11) 7509-16. Journal code: JDF. ISSN: 0270-6474. Pub. country: United States. Language:

English.
AB The axonal regenerative properties of the new immunosuppressant drug **FK506** (**tacrolimus**) are further explored in this continuing study. In an initial report (Gold et al., 1994a), we described the ability of **FK506** to reduce the time until return of function in the hind feet of rats following a sciatic nerve crush. In the present study, we examined the morphological correlate underlying this enhancement of functional recovery. In rats receiving daily subcutaneous injections of **FK506** (1.0 mg/kg) for 18 d following a sciatic nerve crush the regenerating axons appeared larger in size compared to saline-injected control animals. Morphometric analysis of axonal calibers in the soleus nerve demonstrated that mean axonal areas for the largest 30% of axons were increased over axotomized control values by 93% in the **FK506** -treated animals. Next, the rate of axonal regeneration was determined by radiolabeling the L5 dorsal root ganglion (DRG) at 9 and 14 d following axotomy. Regression analysis of the outgrowth distances for sensory axons between 10 and 15 d revealed a 16% increase in regeneration rate. Electron microscopy of intramuscular nerve branches in the interosseus muscles confirmed that the axons in the **FK506**-treated animals were further advanced toward their targets; in some instances, axons were shown to reinnervate muscle spindles. The results are discussed in terms of the known ability of **FK506** to inhibit the activity protein phosphatase 2B (calcineurin).

L45 ANSWER 14 OF 14 CAPLUS COPYRIGHT 1999 ACS DUPLICATE 9
1994:621678 Document No. 121:221678 The immunosuppressant **FK506** increases functional recovery and **nerve regeneration** following peripheral nerve injury. **Gold, Bruce G.**; Storm-Dickerson, Toni; Austin, Daniel R. (Center Research Occupational and Environmental Toxicology, Oregon Health Sciences University, Portland, OR, 97201-3098, USA). Restor. Neurol. Neurosci., 6(4), 287-96 (English) 1994.
CODEN: RNNEEL. ISSN: 0922-6028.
AB Regeneration of peripheral nerve fibers over long distances often requires extended periods of convalescence. Loss to society can be measured in terms of increased health care costs, decreased productivity and, in the case of job-related injuries, larger workers' compensation claims. The availability of drugs to increase axonal regeneration would be beneficial not only to patients but also to society in general by decreasing these costs. In the present paper, the authors present the authors initial studies on the regenerative effects of the new immunosuppressive agent **FK506**. Rats given a sciatic nerve crush (axotomy) received daily s.c. injections of **FK506** (1.0 mg/kg); axotomized control animals received saline. Clin. signs of recovery in the hind feet were manifested two days earlier in **FK506**-treated than in saline-treated animals; movement in the toes, and walking on the hind feet and toes were obsd. at 16 and 17 days, resp., in saline-treated rats and at 14 and 15 days, resp., in **FK506**-treated rats. Measurement of interdigit distances in the hind feet at 18 days following axotomy showed a return toward normal position of the toes (increased interdigit distances) during walking in **FK506**-treated rats. Light and electron microscopy performed at 18 days following axotomy confirmed the clin. appearance of

increased functional recovery in **FK506**-treated rats. Distal to the crush site, the sciatic nerve and its terminal branches from **FK506**-treated animals contained more myelinated fibers compared to saline-treated animals; in the soleus nerve, the nos. of myelinated axons was increased 2.75-fold. Taken together, the present results suggest that **FK506** enhances recovery of function in the rat by increasing the rate of axonal regeneration following a sciatic nerve crush.

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